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Case Report

Chediak-Higashi Syndromein Accelerated Phase: A Case Report

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Abstract: Chediak Higachi Syndrome (CHS) is a very rare autosomal recessive disorder which presents with repeated bacterial infections, albinism, progressive peripheral neuropathy, cranial nerve abnormalities and patients have characteristic silvery grey hair and giant bluish grey granules in cytoplasm of white blood cells. Late stages presents with accelerated phase of this disease which is characterized by lymphohistiocytic infiltration of spleen, liver and lymph nodes. Here, we report a case of one year old child who presented to us in accelerated phase of CHS and diagnosis was made on clinical characteristic findings and presence of largeazurophilic granules in granulocytes and lymphocytes in peripheral blood smear and bone marrow.

Keywords: Chediac-Higashi syndrome, large azurophilicgranules, repeated bacterial infections, albinism, progressive peripheral neuropathy, cranial nerve abnormalities, silvery grey hair accelerated phase, lymphohistiocytic infiltration.

Introduction

Chediak Higashi Syndrome (CHS) is a very rare autosomal recessive disorder, with less than 500 cases published worldwide in about 20 years. [1,8] It is characterized by hypopigmentation of hair, skin and eyes, photosensitivity, bleeding diathesis with history of recurrent skin infections and peripheral neuropathy. It is usually diagnosed by the presence of giant peroxidase positive granules in cytoplasm of neutrophils and rarely in lymphocytes in blood and bone marrow. [1,3,8] Approximately 85% of patients transform into accelerated phase of this disease characterized by pancytopenia, hemophagocytic syndrome and marked lymphocytic infiltration of organs leading to multiple organ failure. [1,3]

Owing to the rarity of the disease we here report a case of Chediakhigashi syndrome in accelerated phase.

Case Report

A one year and three months old child presented in department of pediatrics with complaints of recurrent infections and with history of fever and pallor for past three months. Healso had complaints of abdominal distention for past 2 months. There was no history of bruising or any episode of bleeding and patient had normal bowel habits.

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Physical Examination: Child was conscious, alert and irritable .He had pale looking hypo-pigmented skin and hair with silver- grey color (figure1). On oral examination he was having extensive oral thrush and also had bilaterally enlarged non-tender lymph nodes of cervical and inguinal region. Rest of physical findings including jaundice, clubbing, koilonychia, palmar erythema etc. were absent.

Systemic Examination: On abdominal examination he had a severely distended tense abdomen which was non-tender. Liver was 5cm below right costal margin and spleen was 3cm below left costal margin. In CNS examination he had a GCS of 15/15 with normal tone

and power of both upper and lower limbs and has ataxic gait. Normal sensory and motor functions However rest of systemic findings were unremarkable.

Laboratory Investigations:

Sr.#	Blood CP Parameters	Value	Normal Range
1	Hemoglobin	9 g/dl	14-18 g/dl
2	Red Cell Count	$3.59x10^6$ uL	
3	White Cell Count	$14.1x10^3$/uL	
4	Hematocrit	29.3%	30-40%
5	Platelet Count	118x1000/UL	150-450X1000/UL
6	Reticulocyte Count	8%	0.1-4.0 %
7	Erythrocyte sedimentation rate (ESR)	47mm	0-20 mm

On peripheral blood smear, there was hypochromic microcytic anemia with mild aniosocytosis and moderate polychromasia with prominent lymphocyte population. Also noted were the presence of giant blue-grey granules in the cytoplasm of some neutrophils (figure2a) and lymphocytes (Figure-2b).

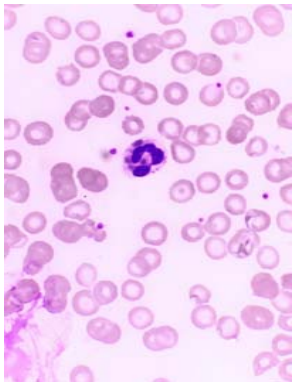

Figure2a: There are giant granules in cytoplasm of neutrophil in peripheral smear

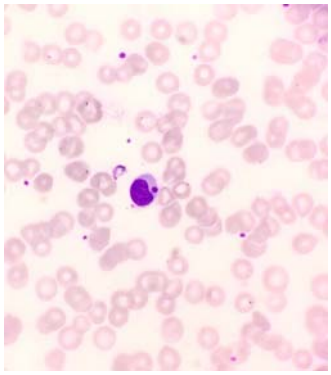

Figure2b: Single giant granule in lymphocyte in peripheral smear

Sr.#	Parameters	Value	Normal Range
Liver function Tests			
1	Alkaline Phosphatase	835IU/L	115-460IU/L
2	Alkaline Tranferase	139IU/L	0-30IU/L
3	Bilirubin	1.3mg/dl	<0.1mg/dl
Lipid Profile			
4	Serum Cholesterol	284mg/dl	40-180mg/dl
5	Triglycerides	389mg/dl	25-125mg/dL
6	High Density Lipoprotein Cholesterol (HDL-Ch)	10mg/dl	35-82 mg/dl
7	Low Density Lipoprotein	196 mg/dl	65-140 mg/dl
Electrolytes			
8	Calcium	0.97mmol/L	2.2-2.7mmol/L
9	Sodium	136mEq/L	135-147mmol/L
10	Potassium	5.57mmol/L	3.5-5.5 mmol/L
Others			
11	Blood Sugar Random	77mg/dl	100-180mg/dl
12	Uric Acid	4.9 mg/dl	2-4 mg/dl
13	Fibrinogen	250mg/dl	200-500mg/dl
14	Ferritin	311ng/ml	6-24ng/Ml
Coagulation Profile			
15	Prothrombin Time	13 sec	12 sec
16	Activated PartialThrombin Time	36 sec	32 sec
17	International Normalized Ratio(INR)	0.94	1.0
18	Bleeding Time	8 min	2-5 min

Radiological Findings: On ultrasound abdomen there was mild to moderate ascites.

Bone Marrow Biopsy Findings: Bone marrow biopsy was done through anterior tibia which showed hyper cellular marrow with moderate erythroid series which was normoblastic with mild megaloblastic changes. Myeloid series was hyperplastic with both mature and early granulocytic precursors present. Megakaryocytes were adequate with normal maturation. There were prominent giant blue-grey granulesin cytoplasm of both mature and immature components of myeloid series (Figure-3,4). Hemophagocytosis was also observed with prominent histiocytes (Figure5). Morphologically these findings were consistent with Chediak Higashi syndrome and hemophagocytosis indicating accelerated phase of the disease.

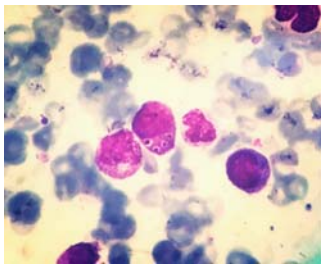

Figure-3: Red arrow indicating giant intracytoplasmic granules in myelocyte.

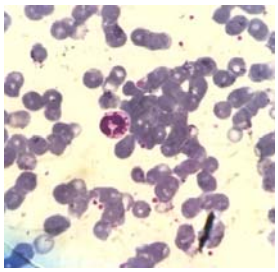

Figure4: Red arrow indicating giant granules in a neutrophil in bone marrow aspirate

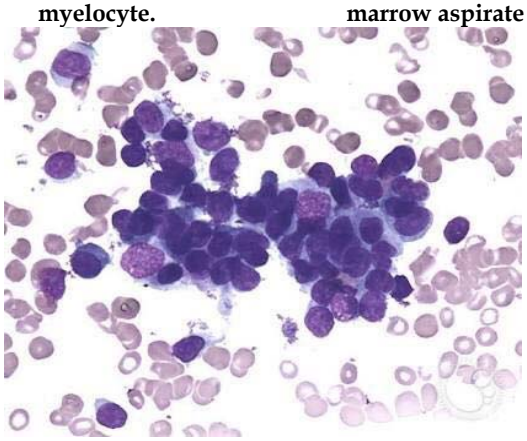

Figure-5: Prominent hemophagocytosis on bone marrow aspirate

Discussion

Chediak Higashi Syndrome is a rare autosomal recessive disorder which is characterized by severe immunodeficiency, recurrent infections, bleeding diathesis, occulocutaneous albinism, late onset neurological manifestations (central and peripheral neuropathies, cerebellar ataxia, sensory loss, muscle weakness, parkinsonism) and lymphoproliferative syndrome. [1,2,3] Mutations in lysosomal trafficking regulator gene *LYST* which encodes for LYST protein have been implicated as the cause of this disease, this gene is located on chromosome 1q42.1-q42.2. [6] This results in defective release of melanin and cytolytic enzymes causing hypopigmentation of hair and skin. Diagnosis of CHS can be done by finding giant intracytoplasmic granules in leukocytes, monocytes, platelets, lymphocytes in blood and bone marrow. [4,7] In 85-90% cases accelerated terminal phase (Hemophagocyticlymphohistiocytosis) occurs characterized by non-malignantlymphohistiocytic infiltration of multiple organs, resulting in severe pancytopenia, organomegaly (liver, spleen), severe infections, bleeding manifestations leading to death of the patient. [3,4,5] in 80% patients death usually occurs in first decade of life. The only treatment available at present is allogenic stem cell transplantation before the onset of accelerated phase. [4]Till now 500 cases have been reported worldwide. [1] Kanjanapongkul S in 2006 reported a case of CHS in one and a half year old child with silverish white hair, hepatosplenomegaly, hypopigmentation of skin and presence of large granules in the cytoplasm of granulocytic series in bone marrow. [2] Shravaniin 2017 and shashikant et al. in 2012 also reported cases of CHS in children who presented with massive hepatosplenomegaly, lymphadenopathy,and abdominal distention, hypopigmentation of hair and skin along with prominent intra cytoplasmic granules in myeloid series with features of hemophagocytosis on bone marrow which showed accelerated phase of disease. [3,4] Similar findings were reported by Bouatay et al. in 2014. [5]

All these characteristic findings were also present in our case of CHS, which was diagnosed on the basis of characteristic clinical findings including hypopigmented hair, albinism, history of recurrent bacterial infections and moreover, presence of giant inclusion bodies in cytoplasm of neutrophils and lymphocytes on peripheral film and also in the myeloid series including monocytes in bone marrow confirmed the diagnosis. Hemophagocytosis was also present with prominent histiocytes on marrow aspirate, indicating the accelerated phase of the disease as clinically hepatosplenomegaly along with lymphadenopathy was also present.

Rudramurthy in 2015 reported 5 cases of CHS from India in which four of them presented in accelerated phase of the disease, and all having giant inclusion bodies in cytoplasm of lymphocytes. [8]Gil-Krzewska

A et al in 2015 did analysis on patients who were diagnosed with CHS concluding that LYST is the gene controls the movement, size, exocytosis of cytotoxic granules and also affects multiple aspects of natural killer cells toxicity. [6] There is no specific treatment for CHS except antibiotic to treat infections, antiviral therapy in accelerated phase and platelet transfusion if serious bleeding occurs and the allogenic stem cell transplantation. [7]

Conclusion

Chediak Higashi Syndrome is rare disorder, therefore, it should be kept in mind while dealing with patients who have the specific clinical findings because it can present with varied spectrum of clinical presentations and investigations. Allogenic stem cell transplantation is the only available treatment, therefore there is a need to diagnose these patients in an early stage, so that transplantation can be done before going to accelerated phase. As, CHS is an autosomal recessive disorder therefore, parental and family counseling is very important.

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E. Critical Review
F. Facilitated for Reagents/Material/Analysis